Artificial blood vessels

A team of researchers at the Laval University School of Medicine in Quebec has developed a technique to manufacture blood vessels in vitro without the need for synthetic scaffolding, which until now has been a necessary, and sometimes problematic, component of tissue engineering in most other tissues. By taking fibroblasts and smooth muscle cells from the skin and superficial veins of a recipient, the scientists were able to grow sheets of progeny cells, which were then rolled into tubes and cultured in a special bioreactor. The resulting veins have the structural and cellular characteristics of natural blood vessels, and because they are derived entirely from the recipient's cells, there is little danger of rejection. The team's findings are reported in a recent issue of the *FASEB Journal* (12:47–56, 1998). "I believe that this new technology has enormous potential for engineering all types of tissues. We can now produce a living scaffolding of various geometry and associate it with various cell types to produce entirely biological living human organs," states Nicolas L'Heureux, who is first author on the study and currently at the University of California, San Diego.

Beef about cloning

In the latest development in animal cloning, a team at the University of Wisconsin-Madison has reported using bovine oocytes as recipients for cloning not only cattle, but also sheep, pigs, rats, and primates. The scientists used adult cells from the ears of donor species, transferred their nuclei into cow eggs, and then attempted to implant the eggs into cattle and sheep. "[W]e had established pregnancies in cattle and in sheep that did not go very far. We could identify conceptus, but could not pick up a heartbeat," says Neal First, who led the effort. While the inability to produce viable offspring was something of a disappointment, the work, reported in January at the International Embryo Transfer Society meeting in Boston, demonstrated that such interspecies cloning is at least conceptually possible. Because only a small number of such transfers have been attempted, First is still optimistic, pointing out that "Dolly was one out of 277." In addition to illuminating the mechanisms of early developmental processes, the finding could lead to more efficient development of donor animals for xenotransplantation or be applied to endangered species recovery programs.

Research News Briefs written by Alexander Castellino, Alan Dove, and Margret Einarson.

Hot leads from worms

Using a newly developed temperature probe, researchers from the University of Delaware, Rutgers University, and Diversa (San Diego, CA) have discovered that the Pompeii worm (*Alvinella pompejana*), a denizen of deep-sea hydrothermal vents, withstands the most extreme temperature gradient ever observed in a living organism. Reporting their results in the February 5 issue of the journal *Nature* (391:545–546, 1998), the scientists show that the anterior end of the worm is nearly 60°C cooler than its posterior end. The worms are also covered with 30–50 different strains of bacterial symbiont, from which the team hopes to isolate enzymes that can tolerate broad temperature ranges. "Together with its symbionts, [the worm is] a tremendous package, not only for eurythermal enzymes, but also the fact that they live in. . .heavy metals," says S. Craig Cary, assistant professor of Marine Studies at the University of Delaware and the lead author on the study. Diversa, which specializes in pursuing extremophilic organisms in extreme environments, is now working to develop the commercial potential of the bacteria. "This is a beautiful example of academia merging with industry," states Cary, who is continuing his research on the worms' biology.

Zinc-based protease inhibitors

A new and unique approach for inhibiting serine proteases like trypsin has been described by a collaboration of researchers at Axys Pharmaceuticals (South San Francisco, CA) and the University of San Francisco (*Nature* 391:608–612, 1998). The authors used a combination of structure-based drug design, crystallographic methods, and enzymology to show that small-molecules like BABIM [bis(5-amidino-2-benzimidazolyl) methane] and its keto derivative inhibit serine proteases by acting as scaffolds onto which ions like Zn^{2+} and Co^{2+} can be tetrahedrally coordinated to increase affinity for trypsin. BABIM alone has a K_i = 19 μM for trypsin, but in presence of subphysiological concentrations of Zn^{2+}, this affinity increases by 3,800 fold, making it a very potent inhibitor. The crystal structure of trysin–BABIM–Zn^{2+} indicates that the amidinobenzene portion of BABIM superimposes exactly onto benzamidine, the classical trypsin inhibitor, in the trypsin–benzamidine crystal structure. BABIM is nontoxic to cells, and its half-maximal lethal dose in mice is 10^4–10^5 fold higher than that required for trypsin inhibition. Brad Katz, the corresponding author on the paper, claims that "Axys has inhibitors more potent and selective than BABIM that will be therapeutically important for targeting proteases playing key roles in diseases like asthma."

Engineered hormone receptor

A long-sought goal of biomedical researchers is to discover a method to exogenously regulate the expression of specific genes. Howard Hughes Medical Institute investigators David Corey and David Manglesdorf and their colleagues at the University of Texas Southwestern at Dallas have now discovered a key component toward realizing this goal (*Chem. Biol.* 5:13–21, 1998). They have engineered a mutant version of a ligand-activated nuclear hormone receptor, the retinoid X receptor (RXR), which is more responsive to a synthetic ligand than to its natural ligand. Nuclear hormone receptors are a family of ligand-activated transcriptional regulators that bind a wide variety of ligands, including retinoic acid, steroid, and thyroid hormones. Surprisingly, only a two amino acid change in the ligand-binding domain was required to change the binding specificity of RXR. "What's unique about this is we have now shown the principle that you can take the ligand-binding domain of a nuclear receptor and alter it so it has an entirely new specificity," says Mangelsdorf. In the future, it may be possible to create transcriptional activators responsive to a variety of synthetic ligands. The ability to alter the binding specificity of the nuclear hormone receptors "may enable us to activate a specific pathway in an animal selectively without any crossover from the endogenous ligand," he adds.